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10/091,357	03/01/2002	Sivaram Pillarisetti	18631-0141 (45115-268551)	7257
26158	7590	11/29/2004	EXAMINER	
WOMBLE CARLYLE SANDRIDGE & RICE, PLLC P.O. BOX 7037 ATLANTA, GA 30357-0037			HADDAD, MAHER M	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/091,357

**Applicant(s)**

PILLARISETTI, SIVARAM

**Examiner**

Maher M. Haddad

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 October 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-5 and 17-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-5 and 17-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/13/02</u> . | 6) <input type="checkbox"/> Other: _____  |

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#### DETAILED ACTION

1. Claims 1, 3-5, 17-24 are pending.
2. Applicant's election without traverse of Group I-XV, claims 1-5 (now claims 1, 3-5 and 17-24) drawn to a method for detecting compounds that affect cell proliferation comprising measuring the amount of HSPG and a molecule as the species of the compounds filed on 10/18/04, is acknowledged.
3. Claims 1, 3-5 and 17-24 are under examination as they read on a method for detecting compounds that affect cell proliferation comprising measuring the amount of HSPG and a molecule as the species of the compounds.

During a telephone conversation with Jeffery Arnold on November 19, 2004, regarding Applicant's election of Groups I-XV, Applicant submits that the instant methods of Groups I-XV are methods for identifying compounds that affect cell proliferation by screening for the HSPG production. In view of the amended claims and applicant argument, the Examiner agreed. Therefore, the pending claims are under examination as they read on a method for detecting compounds that affect cell proliferation comprising measuring the amount of HSPG and a molecule as the species of the compounds.

4. Applicant's IDS, filed 5/13/04, is acknowledged, however, references 14 and 16 were crossed out as the entire documents were not found. Applicant is invited to produce such documents.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claims 1, 3-5 and 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
  - A. Claims 1 and 22-24 provide for measuring the amount of HSPG, perlecan, syndecan and glypican, respectively, but, since the claim does not set forth any steps involved in the endpoint, it is unclear whether increase or decrease in the amount of HSPGs is indicative of cell proliferation. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.
  - B. It is improper to recite "compounds" in claims 1 and 22-24 as the claims should recite the singular form. It is suggested that the word be changed to "a compound". Further, claims 1(a/c), 22(a/c), 23(a/c) and 24(c) recite a/the compound while the preamble of the claims

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recite “compounds”, it is unclear whether the method is detecting compounds or a compound.

- C. Claims 5 and 17-19 are indefinite in the recitation “the compound”, claims 5 and 17-19 depends from claim 1, wherein claim 1 recites “compounds”. Consistency is required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 1, 3-5 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase “unknown cellular proliferative activity” claimed in claims 1 and 22-24, and the phrase “represents a departure from the specification and the claims as originally filed.

Applicant’s amendment filed 10/18/04 does not point to the specification for support for the newly added limitations “unknown cellular proliferative activity” as claimed in claims 1 and 22-24. However, the specification does not provide a clear support for such limitation. It is noted that the specification on page 7, lines 20-21 discloses a compound initially has unknown activity, however, a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads, see *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). The instant claims now recite a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

9. Claims 1, 3-5 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a compound that affect (Smooth Muscle Cell) SMC proliferation comprising adding a compound having unknown activity to a first cell culture, measuring the amount of HSPG in the first cell culture; and comparing the amount of HSPG in the first cell culture to the amount of HSPG in a second cell culture not treated with the compound, the presence of serum, does not reasonably provide enablement for a method for detecting compounds that affect any cell proliferation comprising adding a compound having unknown cellular proliferative activity to a first cell culture; measuring the amount of any HSPG in the first cell culture, and comparing the amount of HSPG in the first cell culture to the amount of any HSPG in a second cell culture not treated with the compound in claim 1, wherein the HSPG is syndecan or glypican in claims 3 and 23-24, wherein the first cell culture and second cell culture are grown in serum-free media in claim 21. The specification does not enable

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any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The claims do not require the presence of conditioned media in the claimed methods, however, Ettenson et al (J Cell Physiol. 2000 Jul;184(1):93-100) teach that endothelial heparan sulfate is necessary but not sufficient for control of vascular smooth muscle cell growth. Ettenson et al teach that HSPG fraction alone could not approach the inhibitory potential of unfractionated conditioned medium from postconfluent EC cultures. Non-PG proteins produced by the endothelial cultures had no effect on vSMC growth on their own. Yet, when they were mixed together with HSPG fractions, from either subconfluent or postconfluent EC cultures, the full growth effects were returned. Non-PG protein fraction from postconfluent cultures with HSPG fractions gave maximal inhibition of vSMC growth, whereas non-PG protein fractions from subconfluent EC cultures with HSPG fractions produced the maximal stimulation. Ettenson et al concluded that the effect does not result from a difference in the antiproliferative heparan sulfate component but rather from non-PG proteins that interact with the heparan sulfates (see abstract in particular). Ettenson finally teach that the difference of growth activity of conditioned medium derived from subconfluent and post confluent endothelial cells is the results, not of a difference in HSPG production, but rather of the interaction of HSPG with different non-PG proteins made by these cells under different cell densities (see page 99, 2<sup>nd</sup> paragraph, line 1-5 in particular). Therefore, it is unclear how the compound would affect the cell proliferation in the absence of the conditioned media.

Further, the specification fails to disclose what type of cells produce syndecan or glypican. The specification fails to teach how measure the amount of either syndecan or glypican in cell culture. Neither does the specification teach how to discriminate between prelecan, syndecan or glypican when measuring the amount of HSPGs.

Further at issue the claimed molecule of claim 5, the specification does not provide guidance the skilled artisan as to what molecules to be screened. While the dictionary provides a meaning for the word molecule as the smallest particle of a substance that retains the chemical and physical properties of the substance and is composed of two or more atoms; a group of like or different atoms held together by chemical forces. However, the specification fails to provide such chemical and physical properties of the claimed molecule.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

11. Claims 1, 3-5, 17, 19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Paka *et al* (abstract Nov. 2, 1999).

Paka *et al* teach a method determine whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that apoE stimulates endothelia production of heparan sulfate (HS) enriched in heparin-like sequences. Further, Paka *et al* teach that given that heparin and HS are potent inhibitors of smooth muscle cell (SMS) proliferation, they determined whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that by adding apoE to confluent SMC, it increased  $^{35}\text{SO}_4$  incorporation into cells by 24% and media by 36%. Paka *et al* teach that the increase in the medium was exclusively due to an increase in HS (2.1 fold) and apoE did not alter chondroitin and dermatan sulfate proteoglycan (PG). While adding apoE to proliferating SMC, it inhibited bFGF/EGF stimulated ( $^3\text{H}$ )thymidine incorporation into DNA by 50%, despite decreasing cell number, apoE increased the ratio of  $^{35}\text{SO}_4$  to ( $^3\text{H}$ )thymidine from 2-3.5 suggesting increased HS per cell. Finally, Paka *et al* teach that analysis of the conditioned medium from apoE stimulated cells revealed that the HSPG increase was in perlecan and apoE also stimulated perlecan mRNA expression by >2 fold. Paka *et al* concluded that the ability of apoE isoforms to inhibit SMC proliferation correlated with their ability to stimulate perlecan production and E2 and E4 were less effective in stimulating perlecan (see the entire abstract in particular).

Claim 5 is included because apoE is considered to be a molecule.

Claim 19 is included because ApoE did not alter (stabilizes production) chondroitin/dermatan sulfate proteoglycan (PG).

The reference teachings anticipate the claimed invention.

12. Claims 1, 3-5, 17, 19-20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Paka *et al* (JBC, Dec. 1999, IDS Ref. No. 22).

Paka *et al* teach a method determine whether the anti-proliferative effect of apoE is due to increased HS production and cell growth. Paka *et al* teach that apoE stimulates endothelia production of heparan sulfate (HS) enriched in heparin-like sequences. Further, Paka *et al* teach that given that heparin and HS are potent inhibitors of smooth muscle cell (SMS) proliferation, they determined whether the anti-proliferative effect of apoE is due to increased HS production. Paka *et al* teach that by adding apoE to confluent SMC, it increased  $^{35}\text{SO}_4$  incorporation into PG in media. Paka *et al* teach that the increase in the medium was exclusively due to an increase in

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HS (2.2 fold) and apoE did not alter chondroitin and dermatan sulfate proteoglycan (PG). While adding apoE to proliferating SMC, it inhibited bFGF/EGF stimulated ( $^3\text{H}$ )thymidine incorporation into DNA by 50%, despite decreasing cell number, apoE increased the ratio of  $^{35}\text{SO}_4$  to ( $^3\text{H}$ )thymidine) from 2-3.6 suggesting increased HS per cell. Finally, Paka *et al* teach that analysis of the conditioned medium from apoE stimulated cells revealed that the HSPG increase was in perlecan and apoE also stimulated perlecan mRNA expression by >2 fold. Paka *et al* teach that an anti-perlecan antibody completely abrogated the antiproliferative effect of apoE (see the entire abstract in particular). Paka *et al* teach that the cells were grown in MEM containing 10% FBS (see page 36404, 1<sup>st</sup> col., lines 2-3, and fig 1 description in particular). Lastly, Paka *et al* teach that cell surface syndecan may be used to determine HSPGs mediating antiproliferative effect of apoE, since it is a signaling receptor and the alterations in the phosphorylation state of syndecan may affect cell growth (see page 36408, 1<sup>st</sup> col., 1<sup>st</sup> paragraph in particular).

Claim 5 is included because apoE is considered to be a molecule.

Claim 19 is included because ApoE did not alter (stabilizes production) chondroitin/dermatan sulfate proteoglycan (PG).

The reference teachings anticipate the claimed invention.

13. Claims 1, 3-5, 17, 19-20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Obunike *et al* (Jan 2000) as is evidenced by Paka *et al*, JBC, IDS Ref. No. 22).

Obunike *et al* teach a method to test whether the expression apoE or LPL would modulate proteoglycan (PG) metabolism in cells. Obunike *et al* teach that apolipoprotein E (apoE) and lipoprotein lipase (LPL), key proteins in the regulation of lipoprotein metabolism, binding with high affinity to heparin and cell-surface heparan sulfate proteoglycan (HSPG). Obunike *et al* teach that two apoE-expressing cells, macrophages and fibroblasts, and LPL-expressing chine hamster ovary (CHO) cells were used to study the effect of apoE and LPL on PG production. Cellular PGs were metabolically labeled with  $^{35}\text{S}$  sulfate for 20, and medium, pericellular PGs and intracellular PGs were assessed. Obunike *et al* teach that the PG levels in all transfected cells increased, 1.6-3 fold when compared with control cells. Obunike *et al* teach that total production assessed with [ $^3\text{H}$ ]glucosamine was also increased. Further, Obunike *et al* teach that addition of exogenous apoE and anti-human apoE antibody to both non-apoE-expressing and apoE-expressing cells did not alter PG production. Obunike *et al* concluded that enhanced gene expression of apoE and LPL increases cellular PG production (see abstract in particular). Finally, Obunike *et al* teach that in the apoE-expressing cells, the larger intracellular and pericellular PG pools led to more PG secretion into the medium (see pg 114, 2<sup>nd</sup> col., under Effects of ApoE expression on PG degradation and figure 5A in particular). Furthermore, Obunike *et al* teach that since more PG was produced by apoE-expressing cells, they tested whether another heparin-binding protein, LPL, would increase cellular PG production. Obunike *et al* assessed PG production in control and LPL-overexpressing CHO cells (Fig. 6 in particular).

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Obunike et al show that LPL-transfected CHO cells had 3-fold more sulfate labeled PGs in cells and in the pericellular pool after 20 hrs. incubation. Obunike et al showed that PG secretion into the medium at the end of a 20-hrs. incubation was 185% more in the LPL-expressing cells (see pages 114-115 under Effects of LPL Expression on PG production in particular). Finally, Obunike et al teach that ApoA1- and ApoB17-expressing cells, there was no increase in PG production (see page 115, 1<sup>st</sup> col., 2<sup>nd</sup> paragraph in particular). Obunike et al teach that the PGs in nontransfected and transfected cells were grown in DMEM containing 10% FBS (see page 112, under PG production).

Claims 3-4 and 22 are included because while Obunike et al is silence with respect to prelecan, however, prelecan is the produced HSPG as is evidenced by Paka et al teaches that apoE isoforms to inhibit cell proliferation correlated with their ability to stimulate perlecan expression/production (see abstract in particular).

The reference teachings anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

15. Claims 1, 3 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (abstract Nov. 2, 1999) or Obunike *et al* in view of Paka *et al* (JBC, Dec. 1999, IDS Ref. No. 22).

The teachings of Paka *et al* (Nov. 1999) and Obunike *et al* have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation of syndecan in claims 3 and 23.

Paka et al (Dec. 1999) teach that demonstration of requirement for cell surface HSPGs in mediating the antiproliferative effect of apoE is difficult as agents that interfere with cell surface HSPGs, such as heparinase, heparin and chlorate, independently inhibit cell proliferation. Paka et al (Dec. 1999) further teach that cell surface syndecan is beginning to be recognized as a signaling receptor and that alterations in the phosphorylation state of syndecan may affect cell growth (see page 36407, 2<sup>nd</sup> col., last paragraph and 36408, 1<sup>st</sup> col., 1<sup>st</sup> paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of syndecan in cell culture as taught by Paka et al (Dec. 1999) in a method of detecting compounds that affect cell proliferation as taught by both Paka (Nov. 1999) and Obunike et al.

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Given the difficulty of measuring cell surface HSPGs in mediating the antiproliferative effect of apoE, due to the presence of interfering agents with cell surface HSPGs, such as heparinase, heparin and chlorate, independently inhibit cell proliferation, one of ordinary skill in the art at the time the invention was made would have been motivated to measure the amount of cell surface syndecan because cell surface syndecan is beginning to be recognized as a signaling receptor and that alterations in the phosphorylation state of syndecan may affect cell growth as taught by Paka *et al* (Dec. 1999).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 1, 3 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paka *et al* (abstract Nov. 2, 1999) or Paka *et al* (Dec. 1999, IDS Ref. No. 22) or Obunike *et al* in view of U.S. Pat. No. 6,306,613.

The teachings of Paka *et al* (Nov. 1999), Paka *et al* (Dec. 1999) and Obunike *et al* have been discussed, *supra*.

The claimed invention differs from the reference teachings only by the recitation of glypican in claims 3 and 24.

The '613 patent teaches that K-glypican is part of a growing family of cell surface heparin sulfate proteoglycans (HSPGs) that play a role in regulating cellular proliferation, differentiation, and migration. The core polypeptide of the HSPGs is typically sulfated and some of these HSPGs have been shown to interact with the leaderless protein FGF-2, which may even facilitate FGF-2 binding with its receptor (see col. 15, lines 19-25 in particular)

Given that glypican plays a role in regulating cellular proliferation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure the amount of glypican as taught by the '613 patent in determining cell proliferation method as taught by Paka *et al* (Nov. & Dec. 1999) and Obunike *et al*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because glypican plays a role in regulating cellular proliferation as taught by the '613 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.


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17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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